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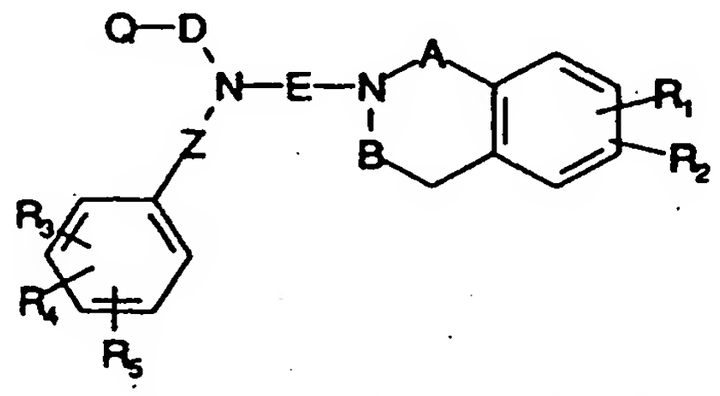
(54) Title: ANTI-ARRHYTHMIC N-SUBSTITUTED 3-BENZAZEPINES OR ISOQUINOLINES

(57) Abstract

A compound of formula (I) or a salt thereof, or a solvate thereof, wherein A represents CH_2, $(CH_2)_2$, CO, $COCH_2$, CH_2CO, $CSCH_2$ or CH=CH; B represents CH_2 or CO; Z represents a bond, CH_2, $(CH_2)_2$ or $X\text{-}CH_2\text{-}CH_2$ wherein X represents O or S; D represents CO, SO_2, NH-CO, $NH\text{-}SO_2$, CH=CH or $P(O)OR_6$ wherein R_6 is $C_{1\text{-}6}$ alkyl; Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, amino, 1-imidazo, alkyl or haloalkyl, or Q represents substituted or unsubstituted: furanyl, pyranyl, thienyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group; R_1, R_2, R_3, R_4 and R_5 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2, R_3, R_4 and R_5 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and E represents $C_{2\text{-}4}$ n-alkylene group wherein each carbon is optionally substituted by R_6; a process for preparing such compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in medicine.



(I)

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ANTI-ARRHYTHMIC N-SUBSTITUTED 3-BENZAZEPINES OR ISOQUINOLINES

The invention relates to certain novel compounds, to pharmaceutical compositions containing such compounds, to a process for the preparation of such compounds and to the use of such compounds as active therapeutic agents.

Anti-arrhythmic agents are classified according to their electrophysiological effects on the cardiac cell (Vaugham-Williams, 1970, 1989) : class I agents block the fast sodium current, class II agents are beta-adrenergic blockers, class III agents block potassium currents, class IV agents block the calcium current, and class V agents are specific sinus node inhibitors.

A majority of ventricular and atrial arrhythmias are related to reentrant circuit. The prolongation of myocardial refractoriness within or surrounding such a reentrant circuit is a potential mechanism for the management of cardiac arrhythmias.

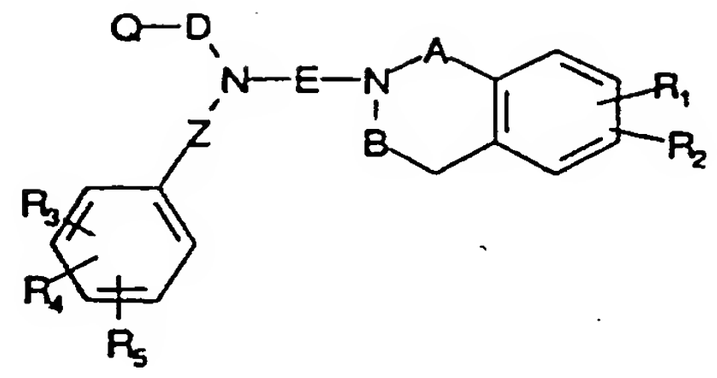
Because class III antiarrhythmic agents block cardiac potassium currents, they prolong the repolarisation process and increase refractoriness. Consequently class III agents represent the most specific class to treat reentrant arrhythmias.

However, due to their mechanism of action, i.e. a concentration dependent increase in the cardiac action potential duration, higher doses of class III antiarrhythmic agents may trigger arrhythmias. Such arrhythmias, called Torsade de Pointe represent the main adverse effect for all pure class III compounds currently in development.

United Kingdom Patent Applications, Publication Numbers 2099425 and 2130213 disclose certain benzazepines and benzodiazines which are stated to have heart rate lowering activity.

It has now been discovered that certain novel N-substituted benzocyclic amine derivatives induce a self-limiting increase of the cardiac action potential duration, related to a dual blockade of cardiac potassium and calcium channels. Consequently, they are considered to be useful anti-arrhythmic agents having an improved pharmacological profile over pure class III anti-arrhythmic agents, in particular they area considered to show a low proarrhythmic potential and readily restore the contractile function of the ischaemic myocardium. They are considered to be particularly useful for the treatment of atrial or ventricular cardiac arrhythmias.

Accordingly, the invention relates to a compound of formula (I) :



(I)

or a salt thereof, or a solvate thereof, wherein

A represents CH_2, $(CH_2)_2$, CO, $COCH_2$,CH_2CO, $CSCH_2$ or CH=CH;

B represents CH_2 or CO;

Z represents a bond, CH_2, $(CH_2)_2$ or X-CH_2-CH_2 wherein X represents O or S;

D represents CO, SO_2, NH-CO, NH-SO_2,CH=CH or $P(O)OR_6$ wherein R_6 is C_{1-6} alkyl;

Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, amino, 1-imidazo, alkyl or haloalkyl, or Q represents substituted or unsubstituted: furanyl, pyranyl, thienyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group;

R_1, R_2, R_3, R_4 and R_5 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2, R_3, R_4 and R_5 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and

E represents C_{2-4} n-alkylene group wherein each carbon is optionally substituted by R_6.

Suitably, A represents CH_2, $(CH_2)_2$, CH_2CO or CH=CH.

Preferably, A represents $(CH_2)_2$.

Suitably, B represents CH_2.

Suitably, Z represents a bond, CH_2 or $(CH_2)_2$.

Preferably, Z represents a bond.

Suitably, D represents CO, SO_2, NH-CO or -CH=CH-.

Suitably, D represents CO or SO_2, preferably CO.

Suitably, Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5, suitably 1 to 3, substituents selected from the list consisting of nitro, halogen, alkylsulfonamido, amino, 1-

imidazo, alkyl or haloalkyl, favourably nitro, halogen or alkylsulphonylamido, preferably nitro.

Suitably, Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted: pyranyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl; indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group.

Suitably, Q represents cycloalkyl optionally fused to an aryl group, for example bicyclo[4.2.0]octa-1,3,5-triene.

Favourably, Q represents aryl, such as phenyl.

Favourably, Q represents substituted furanyl, substituted thienyl or substituted or unsubstituted pyranyl.

Favourably, Q represents the benzo fused equivalents of furanyl or pyranyl; or indolyl.

Favourably, Q represents pyridinyl.

An example of a substituent for Q is a nitro group, a halogen, a methylsulphonamide group or a 1-imidazo group.

Examples of Q include phenyl, 3-nitrophenyl, 4-nitrophenyl, furanyl 5-nitro-2-furanyl, thienyl and bicyclo[4.2.0]octa-1,3,5-triene.

In a preferred aspect, Q is phenyl or substituted phenyl, most preferably nitrophenyl such as 3- or 4-nitrophenyl, preferably 4-nitrophenyl.

Suitably, one or both of R_1 and R_2 represents alkoxy, for example methoxy.

Suitably, one or two of R_3, R_4 and R_5 represents alkoxy, for example methoxy, and the remaining members represent H.

Suitably, E represents $CH_2CH_2CH_2$.

As used herein, the term "alkyl" includes straight or branched chain alkyl groups having from 1 to 12, favourably 1 to 6, carbon atoms and shall include such alkyl groups when forming part of other groups such as alkoxy or arylalkyl groups.

As used herein, the term "alkenyl" includes straight or branched chain alkylene groups having from 2 to 12, favourably 2 to 6, carbon atoms and one or more double bonds.

As used herein, the term "alkynyl" includes straight or branched chain alkylene groups having from 2 to 12, favourably 2 to 6, carbon atoms and one or more triple bonds.

As used herein the term "aryl" includes phenyl and naphthyl, preferably phenyl.

Unless otherwise specified, optional substituents for aryl include up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl,

hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy or alkylcarbonyl groups.

Suitable heteroaryl groups include substituted or unsubstituted, single or fused ring heteroaryl groups having 5 or 6 ring atoms which comprise up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

In particular, the heteraryl group comprises 1, 2 or 3 heteroatoms, in each ring especially 1 or 2, selected from oxygen, sulphur or nitrogen.

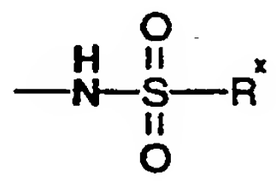
Suitable heteroaryl groups include benzo fused 5 or 6 membered hetero ring, such as indole, benzofuran and benzothiophene groups.

Suitable substituents for the heteroaryl group include the substituents as described herein with regard to the aryl group.

As used herein, the term "cycloalkyl" includes C_{3-8} preferably C_{4-6} cycloalkyl groups.

As used herein "halogen" includes fluorine, chlorine or bromine.

As used herein, the term "alkylsulfonamido" includes a radical of the formula



wherein R^X is an alkyl group.

As used herein, the term "cardiac arrhythmia" relates to any variation from the normal rhythm of heart beat, including, without limitation, sinus arrhythmia, premature heartbeat, heartblock, fibrillation, flutter, tachycardia, paroxysmal tachycardia and premature ventricular contractions.

The compounds of formula (I) may possess a chiral carbon atom (for example when E represents a branched alkylene group) and may therefore exist in more than one stereoisomeric form. The invention extends to any of the stereoisomeric forms, including enantiomers of the compounds of formula (I) and to mixtures thereof, including racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with pharmaceutically acceptable mineral acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto-glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids. Preferably the acid addition salt is a hydrochloride.

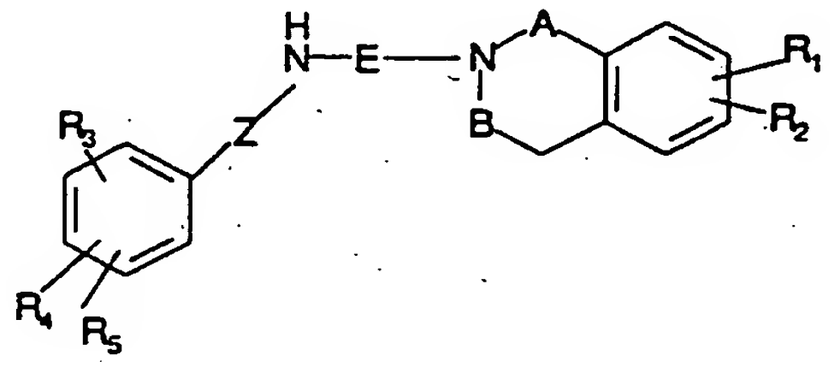
Pharmaceutically acceptable salts also include quaternary salts. Examples of quaternary salts include such compounds quaternised by compounds such as R^y-T wherein R^y is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R^y include methyl, ethyl and *n*- and *iso*- propyl; and benzyl and phenethyl. Suitably T includes halide such as chloride, bromide and iodide.

Pharmaceutically acceptable salts also include pharmaceutically acceptable N-oxides, and the invention extends to these.

The compounds of the formula (I) and their salts may also form solvates, especially pharmaceutically acceptable solvates, such as hydrates, and the invention extends to these, and especially to the pharmaceutically acceptable solvates.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmceutically acceptable salts of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form an aspect of the present invention.

A compound of formula (I) or a salt thereof, or a solvate thereof, may be prepared by reacting a compound of formula (II):



(II)

wherein A, B, Z, E, R_1, R_2, R_3, R_4 and R_5 are as defined in relation to formula (I) with a reagent of formula (III):

$$QL^1 \qquad \text{(III)}$$

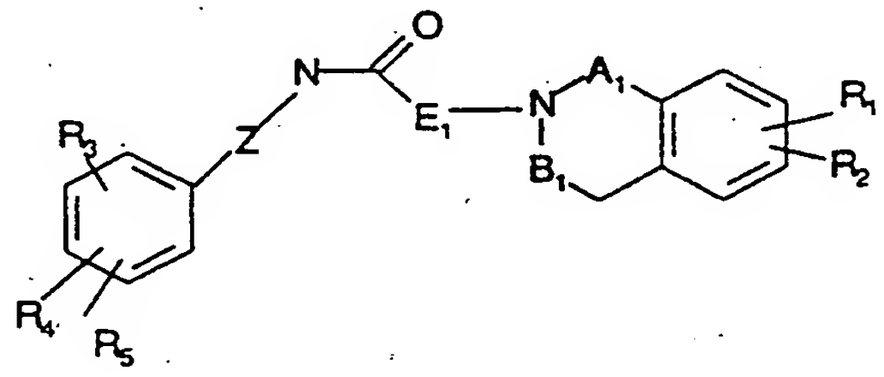
wherein Q is as defined in relation to formula (I) and (a) for compounds of formula (I) wherein D is CO or SO_2, L^1 represents COX or SO_2X respectively wherein X is a leaving group such as a halogen, and (b) for compounds of formula (I) wherein D is NHCO, L^1 is N=C=O; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The reaction conditions for the reaction between compounds of formulae (II) and (III) are conventional conditions appropriate to the nature of the reagent used, generally however the reaction may be carried out in an inert solvent, such as methylene chloride, at any suitable temperature providing a convenient rate of formation of the desired product, generally at a low to ambient temperature, preferably ambient and preferably in the presence of a base such as triethylamine.

The compounds of formula (II) may be prepared by reducing a compound of formula (IV)

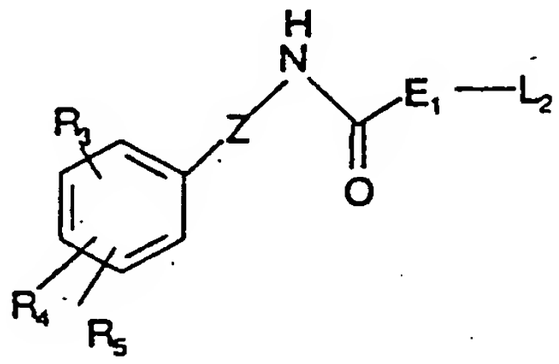


(IV)

wherein Z, R_1, R_2, R_3, R_4 and R_5 are as defined in relation to formula (I), A_1 represents A or a protected form thereof, B_1 represents B or a protected form thereof, and E_1 represents a C_{2-3} n-alkylene chain wherein each carbon atom may be optionally substituted with a C_{1-6} alkyl group; and thereafter if necessary removing any protecting group.

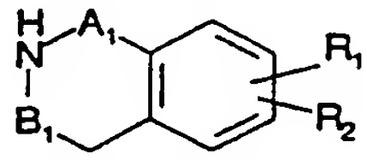
The reduction of the compound of formula (IV) may be effected using any appropriate reduction method, for example metal hydride reduction using a lithium hydride such as lithium aluminium hydride in an aprotic solvent such as tetrahydrofuran (THF), at any suitable temperature which provides a convenient rate of reaction, generally an elevated temperature such as the reflux temperature of the solvent.

A compound of formula (IV) may be prepared by reacting a compound of formula (V):



(V)

wherein Z, E_1, R_3, R_4 and R_5 are as defined in relation to formula (IV), and L_2 is a leaving group or atom such as a mesyl group or a halogen atom, with a compound of formula (VI):



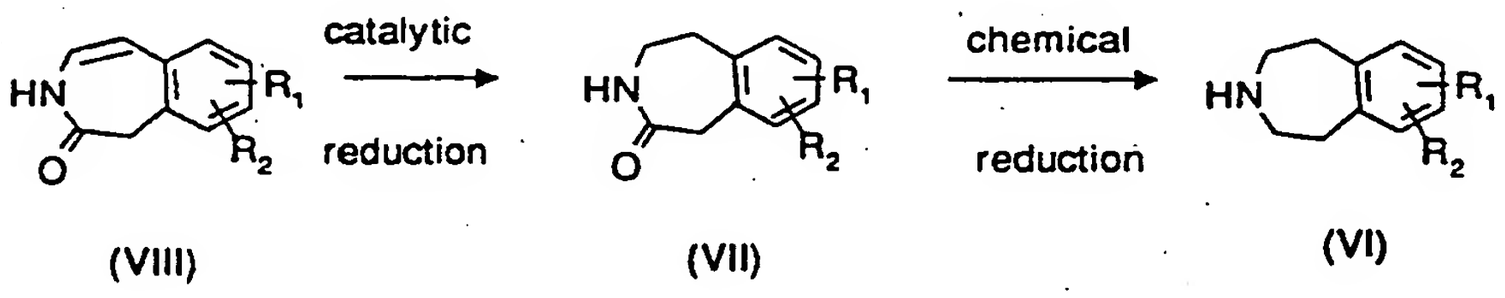
(VI)

wherein A_1, B_1, R_1 and R_2 are as defined in relation to the compound of formula (IV).

The compounds of formula (V) and (VI) are known compounds and may also be prepared according to procedures described in European Patent Application, Publication Number 0471388.

A compound of formula (VI) wherein A_1 represents $(CH_2)_2$ and B_1 is CH_2 - is suitably prepared by the method illustrated in Scheme I:

Scheme I

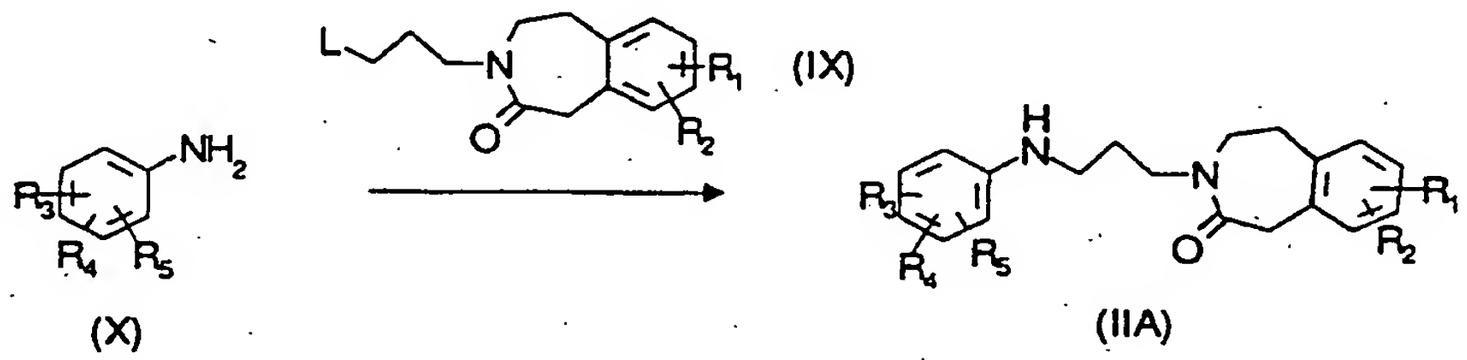


(VIII) (VII) (VI)

The synthesis of compounds of formula (VIII) is described in the literature, for example in J.Med.Chem., 1990, 33, 1496-1504.

The key intermediate for the synthesis of benzazepinone derivative of formula (II) (i.e. B = CO; A $(CH_2)_2$), is best illustrated by Scheme II

Scheme II



(X) (IIA)

Compound (IIA) is then submitted to an acylation as described in the conversion of the compounds of formula (II) to the compounds of formula (I).

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound

of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

More particularly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

A compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

A compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof is normally administered in unit dosage form.

An amount effective to treat the disorder hereinbefore described depends upon such factors as the efficacy of a compound of formula (I) , the particular nature of the pharmaceutically acceptable salt or pharmaceutically acceptable solvate chosen, the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 500 mg for example 2 to 50 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 2,3,4,5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 2500 mg, more usually 50 to 2000 mg, for example 10 to 75mg, that is in the range of approximately 0.002 to 35 mg/kg/day, more usually 1 to 30 mg/kg/day, for example 0.15 to 1 mg/kg/day.

At the above described dosage range, no toxicological effects are indicated for the compounds of the invention.

In such treatment, the compound may be administered by any suitable route, e.g. by the oral, parenteral or topical routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a human or veterinary pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering

agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

For topical administration, the composition may be in the form of a transdermal ointment or patch for systemic delivery of the compound and may be prepared in a conventional manner, for example, as described in the standard textbooks such as 'Dermatological Formulations' - B.W. Barry (Drugs and the Pharmaceutical Sciences - Dekker) or Harrys Cosmeticology (Leonard Hill Books).

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of arrhythmia and/or ischaemic arrhythmia disorders the compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in an amount in the range of from 0.01 mg/kg to 15 mg/kg, for example 0.1 mg/kg to 5 mg/kg, such that the total daily dose for a 70 kg adult will generally be in the range of from 0.7 to 6300 mg, and more usually about 7 to 2100 mg.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

In a further aspect the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of arrhythmia, especially cardiac arrhythmia such as ventricular arrhythmia, and also ischaemic rhythm disorders.

The following Examples illustrate the invention but do not limit it in any way.

Description 1 3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-[(3,4-dimethoxyphenyl)-propanamide

1.22 g (5 mmol) 3-chloro-N-(3,4-dimethoxyphenyl)-propanamide, 1.04 g (5 mmol) 2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepine and 0.61 g (6 mmol) triethylamine in 20 ml acetonitrile were refluxed for 15 hours. The solvent was evaporated and the residue taken up in water. The precipitate was filtered off, washed with water and dried under vacuum to afford 1.7 g (72.4%) of the desired compound.

m.p : 117°C

NMR (DMSO-d_6) : δ = 2.55-3.15 (broad band,12H,6CH_2); 3.71 (s,12H,4CH_3O); 6.79 (s,2H,Ar); 6.87 (d,1H,J=8.7Hz,Ar); 7.09 (dd,1H,J=8.7Hz,J'=2.1Hz,Ar); 7.30 (d,1H,J'=2.1Hz,Ar); 10.04 (s,1H,exch D_2O,NH) ppm.

Description 2 3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine

2.0 g (4.8 mmol) 3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-[(3,4-dimethoxyphenyl)propanamide (D1) and 0.28 g (7.5 mmol) of lithium aluminium hydride in 25 ml THF were refluxed for 5 hours. After cooling with ice water, 0.30 ml water then 0.30 ml 15% aqueous NaOH and 1 ml water were added dropwise. The reactional mixture was filtered through celite and concentrated to dryness. The residue was chromatographed on silica and eluted with ethyl acetate/triethylamine : 95/5 then crystallised from diisopropyl ether yielding 1.0 g (52%) of the desired compound.

m.p : 90°C

NMR ($CDCl_3$) : δ = 1.83 (q,2H,J=6.3Hz,CH_2); 2.05-2.67 (m,6H,3CH_2); 2.86-2.90 (m,4H,2CH_2); 3.18 (t,2H,J=6.3Hz,CH_2); 3.84 (t,12H,4CH_30); 6.16 (dd,1H,J=2.3Hz,J'=8.5Hz,Ar); 6.25 (d,1H,J=2.3Hz,Ar); 6.65 (s,2H,Ar); 6.76 (d,1H,J'=8.5Hz,Ar) ppm.

Description 3 4,5-Dihydro-7,8-dimethoxy-3-[3-[(3,4-dimethoxyphenyl)-(phenylmethyl)-amino]propyl]-1H-3-benzazepin-2(3H)-one

0.42g (1.4 mmol) 7,8-Dimethoxy-3-(3-chloropropyl)-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 1.02 g (4.2 mmol) N-(3,4-dimethoxyphenyl)benzenemethanamine were heated at 100°C under stirring for 1.5 hours. The mixture was cooled and taken up in ethyl acetate. The organic solution was washed twice with 20 ml water then extracted three times with 20 ml of N aqueous hydrochloric acid. The aqueous phase was washed with ethyl acetate, basified with 30% aqueous sodium hydroxide and extracted three times with 20 ml ethyl acetate. The resulting organic solution was washed with water, dried over

$MgSO_4$ and concentrated to dryness. The residue obtained was chromatographed on silica and eluted with methylene chloride/methanol : 98/2 giving 0.28g (39.5%) of a brown oil.
NMR ($CDCl_3$) : δ = 1.87 (m,2H,CH_2); 2.98 (m, 2H,CH_2); 3.32 (m,2H,CH_2); 3.46 (m,2H,CH_2); 3.62 (m,2H,CH_2); 3.75 (s,3H,CH_3O); 3.80 (s,3H,CH_3O); 3.82 (s,3H,CH_3O); 3.84 (s,3H,CH_3O); 3.75-3.85(m,2H,CH_2CO); 4.41(s,2H,ArCH_2); 6.24 (d,1H,J=8.4Hz,Ar); 6.34 (s,1H,Ar); 6.52 (s,1H,Ar); 6.59 (s,1H,Ar); 6.73 (d,1H,Ar); 7.25 (m,5H,Ar) ppm.

Description 4 4,5-Dihydro-7,8-dimethoxy-3-[3-[(3,4-dimethoxyphenyl)-amino]propyl]-1H-3-benzazepin-2(3H)-one
1.6 g (3.2 mmol) 4,5-Dihydro-7,8-dimethoxy-3-[3-[(3,4-dimethoxyphenyl)-(phenylmethyl)-amino]propyl]-1H-3-benzazepin-2(3H)-one (D3) in 50 ml methanol and 6 ml acetic acid were hydrogenated at room temperature under one bar of hydrogen over 0.2 g of 10% palladium on charcoal. The catalyst was filtered off and the solvent evaporated under vacuum. The residue obtained was taken up in water, the aqueous mixture was basified with 30% aqueous sodium hydroxide then extracted twice with 100 ml ethyl acetate. The organic solution was washed with water, dried over $MgSO_4$ and concentrated to dryness to afford 1.23 g (92.7%) of the desired compound.
NMR ($CDCl_3$) : δ = 1.75-1.95 (m,2H,CH_2); 2.95-3.15(m,4H,2CH_2); 3.65-3.75 (t,2H,J=6.5Hz,CH_2); 3.72 (t,2H,J=6.5Hz,CH_2); 3.80-4.00(m,14H,4.00, CH_2); 6.13 (dd,1H,J=2.5Hz,J'=8.5Hz,Ar); 6.25 (d,1H,J=2.5Hz,Ar); 6.55 (s,1H,Ar); 6.60 (s,1H,Ar); 6.72 (d,1H,J'=8.5Hz,Ar) ppm.

Description 5 3-(6,7-Dimethoxy-1,2,3,4,-tetrahydro-2-isoquinolinyl)-N-(3,4-dimethoxyphenyl)-propanamide
2.3 g (10 mmol) 6,7-Dimethoxy-1,2,3,4,-tetrahydro-2-isoquinoline, hydrochloride, 2.43 g (10 mmol) 3-chloro-N-(3,4-dimethoxyphenyl)-propanamide and 2.43 g (24 mmol) triethylamine in 40 ml acetonitrile were refluxed under stirring for 18 hours. The solvent was evaporated and the resulting residue taken up in water. The aqueous mixture was extracted with methylene chloride, the organic solution was washed with water, dried over $MgSO_4$ and concentrated to dryness. The obtained residue was triturated in diethyl ether to afford 3.55 g (88.6%) of the desired compound.
m.p : 131°C
NMR ($CDCl_3$) : δ = 2.61 (t,2H,J=6.1Hz,CH_2); 2.85-2.98 (broad band,6H,3CH_2); 3.72 (s,5H,ArCH_2 and CH_3O); 3.81 (s,3H,CH_3O); 3.85 (s,3H,CH_3O); 3.87

(s,3H,CH_3O); 6.56 (s,1H,Ar); 6.65 (s,1H,Ar); 6.72 (s,2H,Ar); 7.18 (s,1H,Ar); 11.07(s,1H,exch D_2O,NH) ppm

Description 6 3-(6,7-Dimethoxy-1,2,3,4,-tetrahydro-2-isoquinolinyl)-N-(3,4-dimethoxyphenyl)-propanamine

3.4 g (8.5 mmol) 3-(6,7-Dimethoxy-1,2,3,4,-tetrahydro-2-isoquinolinyl)-N-(3,4-dimethoxyphenyl)-propanamide were added by small fractions to a suspension of 0.48 g (13 mmol) lithium aluminium hydride in 40 ml of dried tetrahydrofuran at room temperature and under stirring. The mixture was refluxed under stirring for 3 hours then cooled with ice water. 0.5 ml water then 0.5 ml of 15% aqueous sodium hydroxide then 1.5 ml water were successively added dropwise to destroy the hydride in excess. A precipitate was filtered off, wash with tetrahydrofuran and the resulting organic solution was concentrated to dryness. The residue obtained was chromatographed on silica and eluted with methylene chloride/triethylamine : 95/5 to afford 2.8 g (85.2%) of orange oil.

NMR ($CDCl_3$) : δ = 1.90 (q,2H,J=6.6Hz,CH_2); 2.45-3.05(broad band,1H,exch D_2O,NH); 2.67(t,2H,J=6.6Hz,CH_2); 2.75(d,2H,J=5.2Hz,CH_2); 2.84(d,2H,J=5.2Hz,CH_2); 3.20(t,2H,J=6.6Hz,CH_2); 3.57(s,2H,ArCH_2N); 3.77 (s,3H,CH_3O); 3.79 (s,3H,CH_3O); 3.83 (s,3H,CH_3O); 3.85 (s,3H,CH_3O); 6.11 (dd,1H,J=2.6Hz,J'=8.4Hz,Ar); 6.16 (d,1H,J=2.6Hz,Ar); 6.52 (s,1H,Ar); 6.61 (s,1H,Ar); 6.73 (d,1H,J'=8.4Hz,Ar) ppm.

Description 7 1,3-Dihydro-7,8-dimethoxy-3-[[2-[4-[2-(2-methyl)propyl]phenyl]ethylamino]propyl]-2H-3-benzazepin-2-one.

The title compound was obtained by reacting 2-[4-[2-(2-methyl)propyl]phenyl]ethanamine with 3-(3-chloropropyl)-1,3-dihydro-7,8-dimethoxy-2H-3-benzazepin-2-one, using a procedure similar to that described in description 3.

Description 8 1,3,4,5-Tetrahydro-7,8-dimethoxy-3-[[2-[4-[2-(2-methyl)propyl]phenyl]ethylamino]propyl]-2H-3-benzazepin-2-one.

The title compound was obtained by submitting the compound of description 7 to catalytic reduction over Pd/C.

Description 9 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[2-[4-[2-(2-methyl)propyl]phenyl]ethyl]-1H-3-benzazepin-3-propanamine.

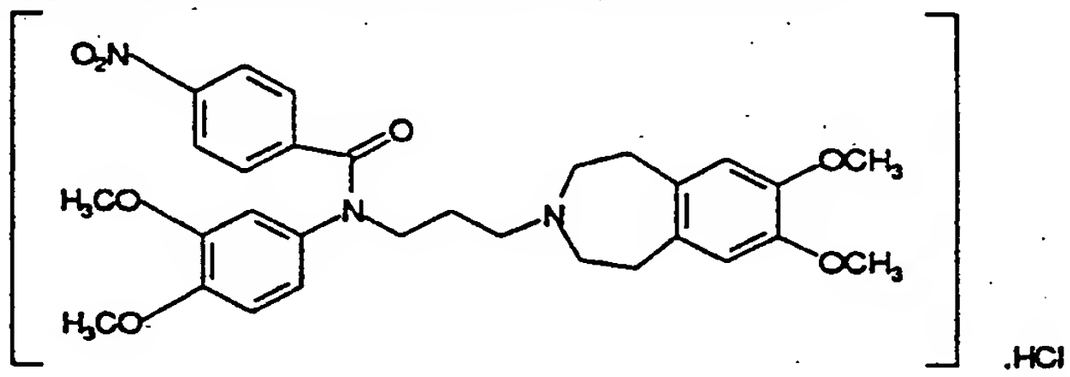
The title compound was obtained by reduction of the compound of description 8, using lithium aluminium hydride and a procedure identical to that of description 2.

Description 10 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[(3,5-dimethoxy)phenylmethyl]-1H-3-benzazepine-3-propanamine.
The title compound was obtained in two steps, starting from 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine and 1-chloro-N-[(3,4-dimethoxy)phenylmethyl]propanamide and following a reaction cascade similar to that described in descriptions 1 and 2.

Description 11 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[[2-(3,4-dimethoxy)phenoxy]ethyl]-1H-3-benzazepin-3-propanamine.
The title compound was obtained by reacting 3-[(3-chloro)propyl]-1H-3-benzazepine with [2-(3,4-dimethoxy)phenoxy]ethylamine using a procedure similar to that described in description 3.

Description 12 1,3-Dihydro-7,8-dimethoxy-3-[[(3,4-dimethoxy)phenyl]aminopropyl]-2H-3-benzazepine-2-one.
The title compound was obtained by reacting 3-(3-chloropropyl)-1,3-dihydro-7,8-dimethoxy-2H-3-benzazepin-2-one with (3,4-dimethoxy)benzeneamine using a procedure similar to that described in description 3

Example 1 N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide, hydrochloride

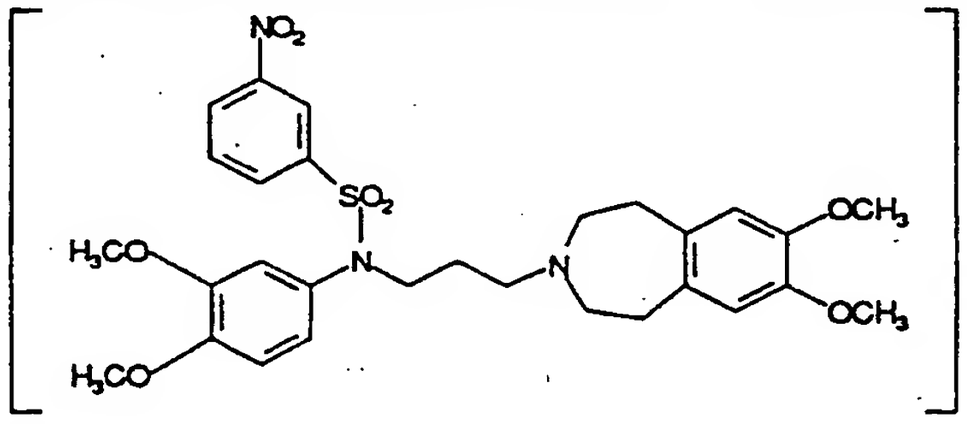


.HCl

0.26 g (1.43 mmol) 4-nitrobenzoyl chloride were added dropwise to a stirred solution of 0.5 g (1.25 mmol) 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 0.45 g (1.43 mmol) triethylamine in 15 ml methylene chloride cooled with ice water. The mixture was stirred for 3 hours at room temperature then washed with water and dried over $MgSO_4$. The solvent was concentrated to dryness. The residue was chromatographed on silica and eluted with methylene chloride/methanol : 95/5 yielding 0.61 g of compound which was salified in methanol by adding 0.25 ml of a solution of hydrochloric acid in diethyl ether. The

methanolic mixture was concentrated to dryness and the residue triturated in anhydrous diethyl ether to afford 0.62 g (84.6%) of the desired compound.
m.p : 247°C
NMR (DMSO-d_6) : δ = 2.03 (m,2H,CH_2); 2.80-3.05 (m,4H,2CH_2); 3.10-3.40 (m,4H,2CH_2); 3.50-3.75 (m,2H,CH_2); 3.68 (s,6H,2CH_3O); 3.73 (s,6H,2CH_3O); 3.90 (t,2H,CH_2N-CO); 6.77 and 6.86 (2s,4H,Ar); 6.98 (s,1H,Ar); 7.56 (d,2H,J=8.5Hz,Ar); 8.08 (d,2H,J=8.5Hz,Ar); 10.76 (s,1H,exch D_2O,NH) ppm.

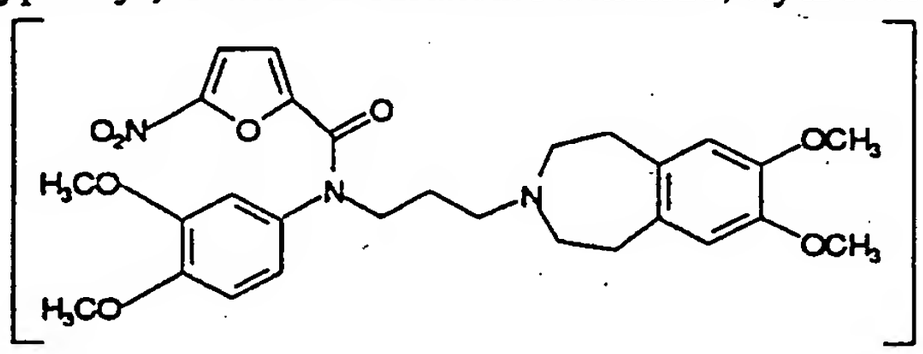
Example 2 N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3-nitrobenzenesulfonamide, hydrochloride.



.HCl

Starting from 138 mg (0.625 mmol) 3-nitrobenzenesulfonylchloride and 200 mg (0.50 mmol) 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and following the method described in Example 1, 215 mg (68.1%) of the desired compound were obtained as yellow crystals. The compound was purified as a free base by chromatography on silica using methylene chloride/methanol : 99.5/0.5 as eluent. The hydrochloride was purified by trituration in diisopropyl ether.
m.p : 214°C
NMR (DMSO-d_6) : δ = 1.83 (m,2H,CH_2); 2.84-3.00 (m,4H,2CH_2); 3.19-3.24 (m,4H,2CH_2); 3.61-3.77 (s,12H,4CH_3O and m,4H,2CH_2); 6.64 (d,1H,J=2Hz,Ar); 6.71 (dd,1H,J=2Hz,J'=8.6Hz,Ar); 6.84 (s,2H,Ar); 6.94 (d,1H,J'=8.6Hz,Ar); 7.86-7.99 (m,2H,Ar); 8.26 (s,1H,Ar); 8.57 (d,1H,J'=7.6Hz,Ar); 10.65 (s,1H,exch D_2O,NH^+) ppm.

Example 3 N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-5-nitro-2-furancarboxamide, hydrochloride.



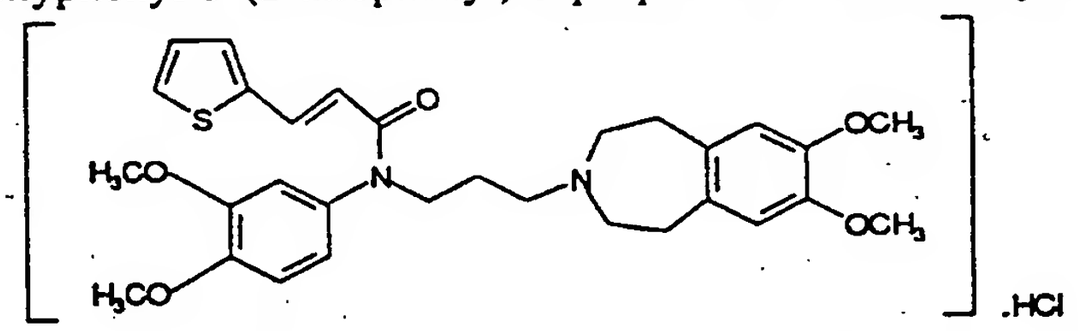
.HCl

Starting from 110 mg (0.625 mmol) 5-nitrofurancarbonyl chloride and 200 mg (0.5 mmol) 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and following the method described in Example 1, 239 mg (68%) of the desired compound were obtained as yellow crystals. The compound was purified as a free base by chromatography on silica using methylene chloride/methanol : 95/5 as eluent. The hydrochloride was purified by trituration in diisopropyl ether.

m.p = 235°C

NMR (DMSO-d_6) : δ = 2.02 (m,2H,CH_2); 2.86-2.94 (m,4H,2CH_2); 3.10-3.40 (m,4H,2CH_2); 3.55-3.90 (3s,12H,4CH_3O and m,4H,2CH_2); 5.82 (d,1H,J=3.5Hz,Ar); 6.85 (s,2H,Ar); 6.99 (s,2H,Ar); 7.12 (s,1H,Ar); 7.51 (d,1H,J=3.5Hz,Ar); 10.74 (s,1H,exch D_2O,NH^+) ppm.

Example 4 N-[3-(78-Dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl-3-(2-thiophenyl)-3-propenecarboxamide hydrochloride



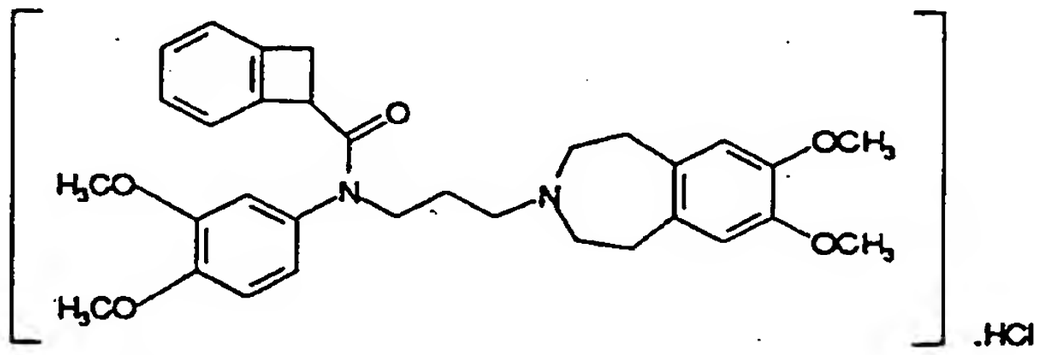
108 mg (0.625 mmol) 3-(2-Thienyl)-2-propenoyl chloride were added to 200 mg (0.50 mmol) 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 0.09 ml (65.7 mg, 0.65 mmol) triethylamine in 10 ml chloroform cooled with ice-water under stirring. The mixture was stirred for 48 hours at room temperature and the solvent was then concentrated to dryness. The residue was chromatographed on silica and eluted with methylene chloride/methanol 95/5 then crystallised by trituration in diisopropyl ether yielding 267 mg of white crystals. The obtained crystallised compound was salified in a mixture of methanol (2 ml) and methylene chloride (1 ml) by adding 0.090 ml of a solution of 5 N hydrochloric acid in diethyl ether. The solvent was concentrated to dryness and the residue triturated in diethyl ether then crystallised from ethyl acetate containing some methylene chloride to afford 155 mg (53%) of the desired compound.

m.p = 242°C

NMR (DMSO-d_6) : δ = 2.85-3.05 (m,2H,CH_2); 3.80-4.05 (m,4H,2CH_2); 4.05-4.30 (m,4H,2CH_2); 4.45-4.70(m,4H,2CH_2); 4.68 (s,6H,2CH_3O); 4.74 (s,3H,CH_3O); 4.77 (s,3H,CH_3O); 7.01 (d,1H,J=15.3Hz, CH=); 7.80-7.95 (m,3H,Ar); 7.95-8.10

(m,3H,Ar); 8.31 (d,1H,J=3.2Hz,Ar); 8.51 (d,1H,J=5.0Hz, CH=); 8.62 (d,1H,J=15.3Hz,Ar); 11.45 (s,1H,exch D_2O,NH^+) ppm.

Example 5 N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-7-bicyclo[4.2.0]octa-1,3,5-trienecarboxamide, hydrochloride.



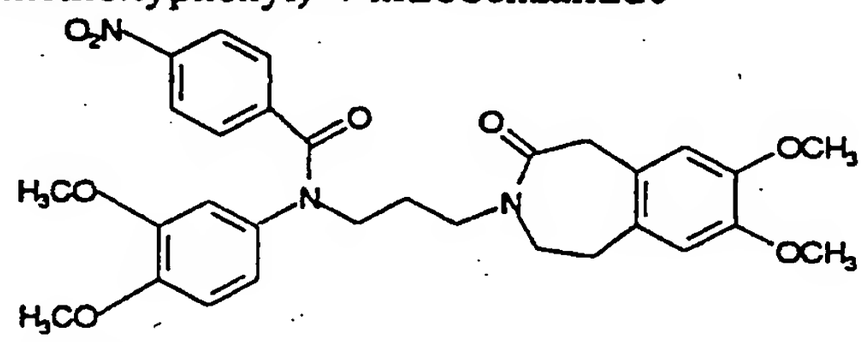
.HCl

Starting from 95 mg (0.57 mmol) bicyclo [4.2.0] octa-1,3,5-triene-7-carbonyl chloride and 200 mg (0.50 mmol) 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl)propanamine (D2) and following the method described in Example 1, 230 mg (80%) of the desired compound were obtained as cream crystals.The compound was purified as a free base by chromatography on silica using methylene chloride/methanol : 95/5 as eluent. The hydrochloride was purified by trituration in diisopropyl ether.

m.p = 217°C

NMR ($CDCl_3$) : δ = 2.20-2.40 (m,2H,CH_2); 2.65-2.90 (m,4H,2CH_2); 3.00-3.50 (m,4H,2CH_2); 3.60-4.00 (m,6H_3CH_2); 3.85 (s,6H,2CH_3O); 3.91 (s,3H,CH_3O); 4.00 (s,3H,CH_3O); 4.21-4.24 (m,1H,CH-CO); 6.64 (s,2H,Ar); 6.95-7.21 (m,7H,Ar); 12.75 (s,1H,exch D_2O,NH^+) ppm.

Example 6 N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide



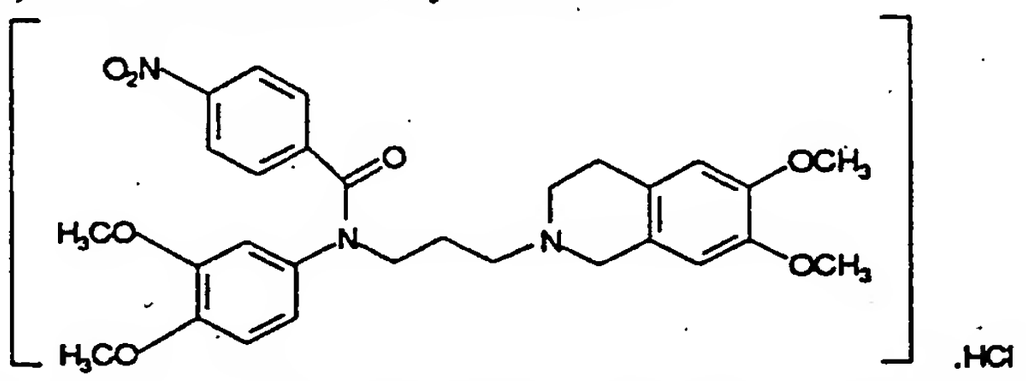
0.8 g (4.3 mmol) 4-nitrobenzoyl chloride in 5 ml chloroform was added dropwise to a stirred solution of 1.18 g (2.8 mmol) 4,5-dihydro-7,8-dimethoxy-3-[3-[(3,4-dimethoxyphenyl)amino]propyl]-1H-3-benzazepin-2(3H)-one (D4) and 0.32 g (3.1 mmol) triethylamine in 30 ml chloroform, cooled with ice water. The mixture was stirred for 4 hours at room temperature and 100 ml methylene chloride were then added. After washing twice with 50 ml N aqueous hydrochloric acid, twice with 50 ml N aqueous sodium hydroxide then twice with 50 ml water, the organic solution

was dried over $MgSO_4$ and concentrated to dryness. The resulting residue was chromatographed on silica and eluted with methylene chloride/methanol : 98/2 to give 1.04 g of compound. The compound was then triturated in a mixture of 5 ml methanol and 50 ml diethyl ether then crystallised from methanol to afford 0.91 g (58%) of yellow crystals.

m.p = 126°C

NMR ($CDCl_3$) : δ = 1.93 (q,2H,J=7.1Hz,CH_2); 3.07 (m,2H,CH_2); 3.56 (t,2H,J=7.1Hz,CH_2); 3.73 (s,3H,CH_3O); 3.81 (s,3H,CH_3O); 3.83 (s,3H,CH_3O); 3.85 (s,3H,CH_3O); 3.73-3.85 (m,4H,2CH_2); 3.92 (t,2H,J=7.1Hz,CH_2); 6.55-6.68 (m,5H,Ar); 7.44 (d,2H,J=8.7Hz,Ar); 8.02 (d,2H,J=8.7Hz,Ar) ppm.

Example 7 N-3-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide, hydrochloride



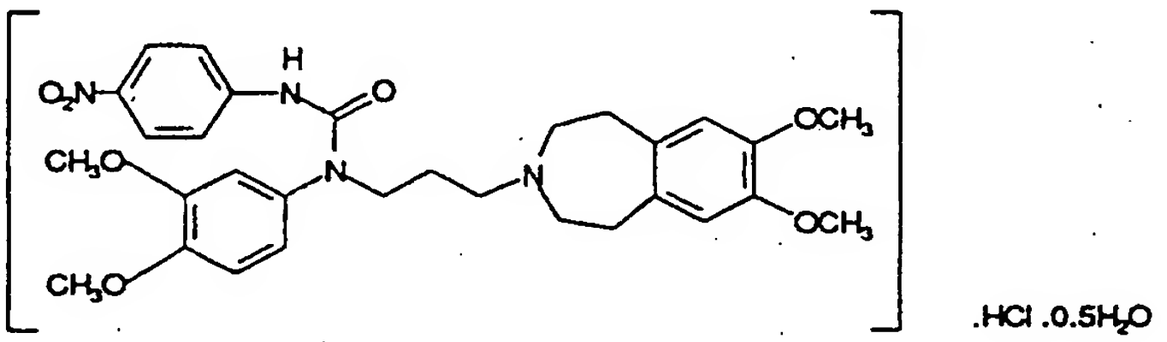
Starting from 1.43 g (7.7 mmol) 4-nitrobenzoyl chloride and 2.7 g (7 mmol) 3-(6,7-dimethoxy-1,2,3,4,-tetrahydro-2-isoquinolinyl)-N-(3,4-dimethoxyphenyl)-propanamine (D6) and following the method described in Example 1, 2.26 g (56.4%) of the desired compound were obtained as yellow crystals after crystallisation from 25 ml acetone.

m.p = 229°C

NMR (DMSO-d_6) : δ = 2.0-2.2 (broad band,2H,CH_2); 2.87-2.94 (broad band,1H,CH_2); 3.14-3.2 (broad band,2H,CH_2); 3.2-3.35 (broad band,1H,CH_2); 3.67 (s,3H,CH_3O); 3.69 (s,3H,CH_3O); 3.72(s,3H,CH_3O), 3.74 (s,3H,CH_3O); 3.67-3.74 (broad band,2H,CH_2); 3.9-4.0 (broad band,2H,CH_2); 4.1-4.3 (broad band,1H,CH_2); 4.3-4.5 (broad band,1H,CH_2); 6.78 (s,3H,Ar); 6.82 (s,1H,Ar); 7.00 (s,1H,Ar); 7.58 (d,2H,j=8.6Hz,Ar); 8.09 (d,2H,J=8.6Hz,Ar); 10.87 (s,1H,exch D_2O,NH^+) ppm.

The following compounds were prepared using methods analogous to those described hereinbefore:

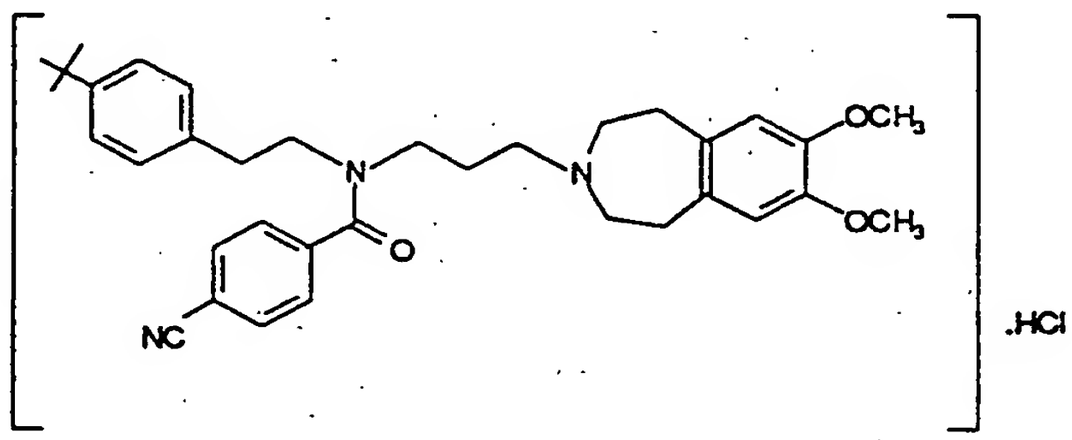
Example 8 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-N'-(4-nitrophenyl)-urea, hydrochloride, hemihydrate



.HCl .0.5H2O

Reacting 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl)propanamine (D2) with 4-nitro-isocyanatobenzene in methylene chloride during one night, followed by a standart work-up, a purification by chromatography on silica gel and a salification by anhydrous hydrochloric acid following procedures similar to those of example 1,afforded the title compound.
m.p. ~160°C

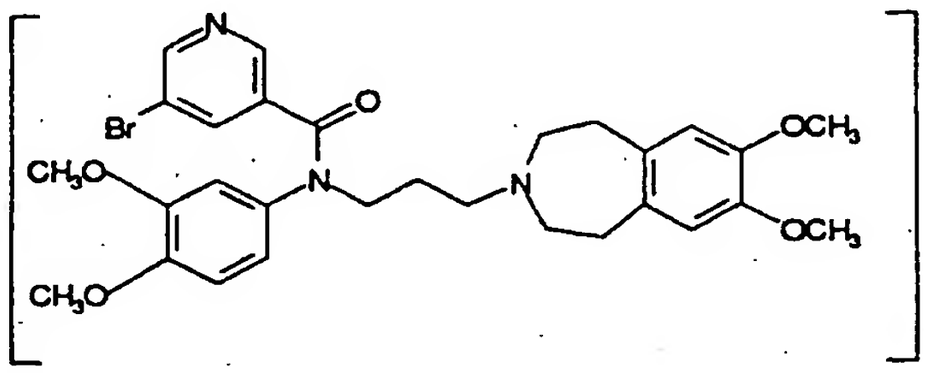
Example 9 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-[2-[4-[2-[2-methylpropyl)]phenyl]ethyl]-4-cyanobenzamide, hydrochloride



.HCl

Starting from 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[2-[4-[2-(2-methyl)propyl]phenyl]ethyl]-1H-3-benzazepin-3-propanamine (D9) and 4-cyano benzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 215 - 217°C

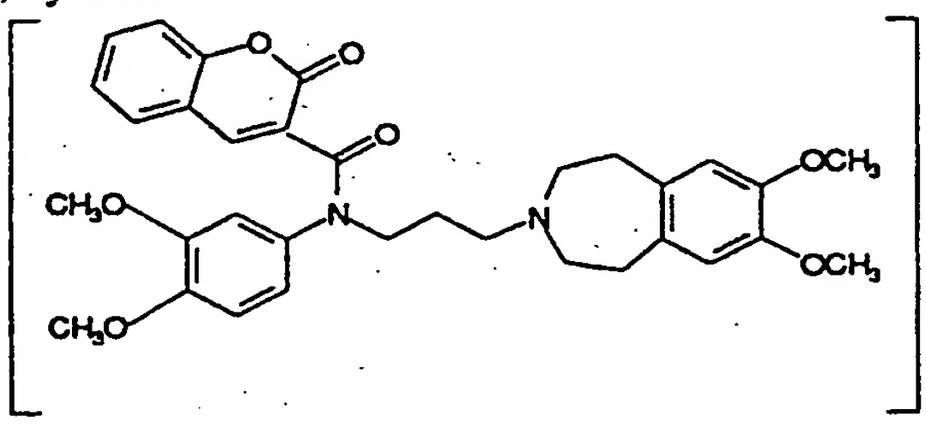
Example 10 5-Bromo-N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-3-pyridinecarboxamide, hydrochloride, hemihydrate



.HCl .0.5H2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 5-bromo-3-piperidinecarbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 239°C

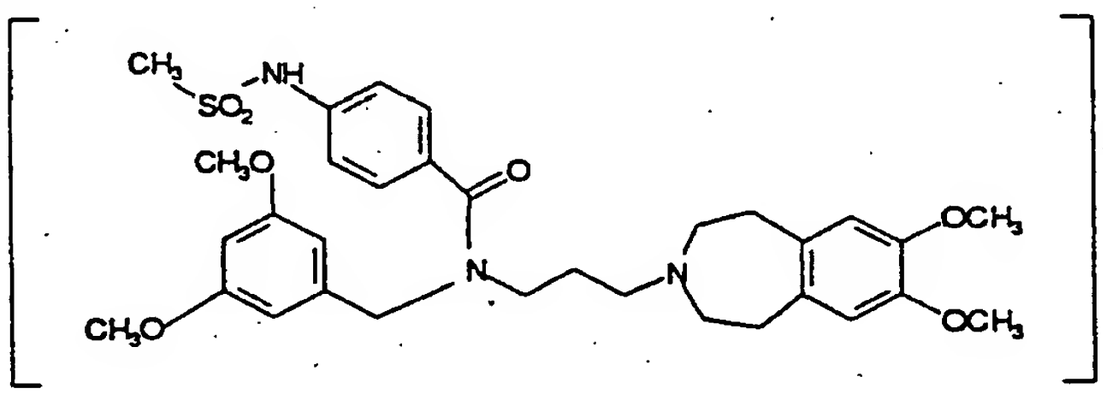
Example 11 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-2-oxo-2H-3-benzopyrancarboxamide, hydrochloride, hydrate



.HCl .H2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 3,4-dihydro-2-oxo-2H-benzopyran-3-carbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 252°C

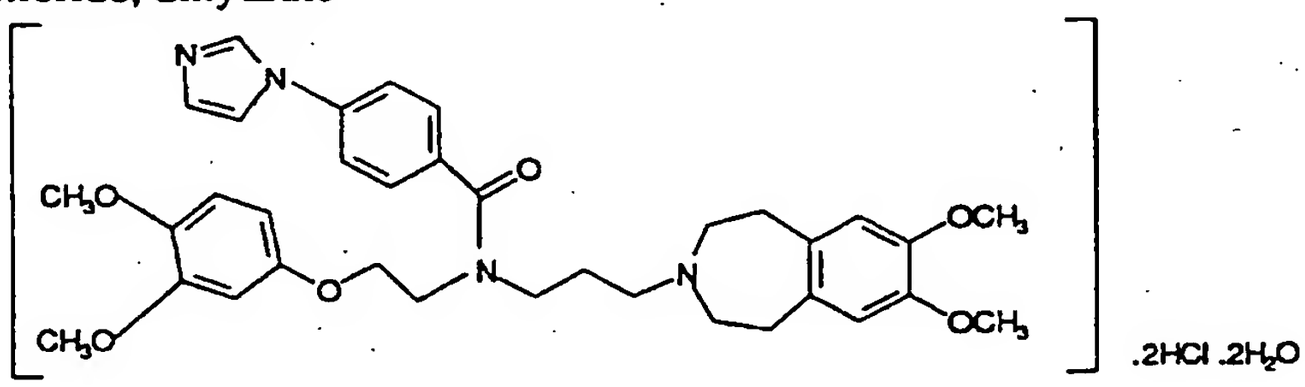
Example 12 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-[(3,5-dimethoxyphenyl)methyl]-4-methylsulphonylaminobenzamide, hydrochloride



.HCl

Starting from 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[(3,5-dimethoxy)phenylmethyl]-1H-3-benzazepine-3-propanamine (D10) and 4-(methylsulfonylamino)-benzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. ~ 135°C

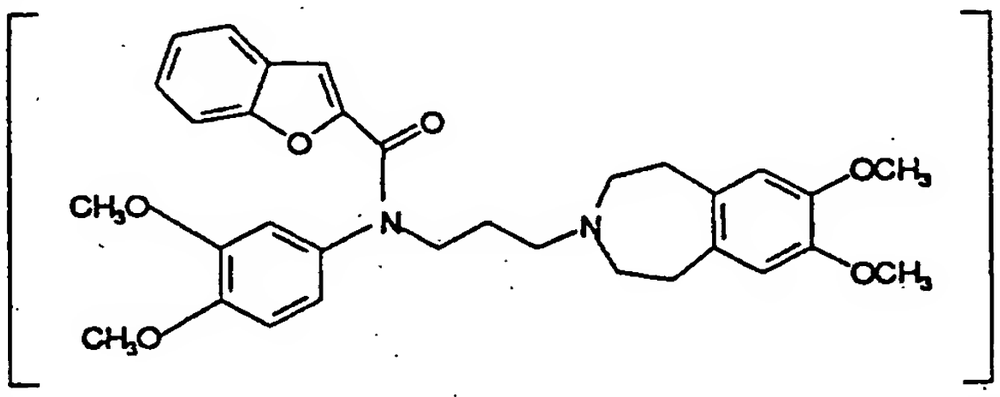
Example 13 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-[2-(3,4-dimethoxyphenyl)oxy]ethyl]-4-(1H-imidazol-1-yl)benzamide, dihydrochloride, dihydrate



.2HCl .2H2O

Starting from 2,3,4,5-Tetrahydro-7,8-dimethoxy-N-[[2-(3,4-dimethoxy)phenoxy]ethyl]-1H-3-benzazepin-3-propanamine (D11) and 4-(1H-imidazo-1-yl)-benzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 150°C

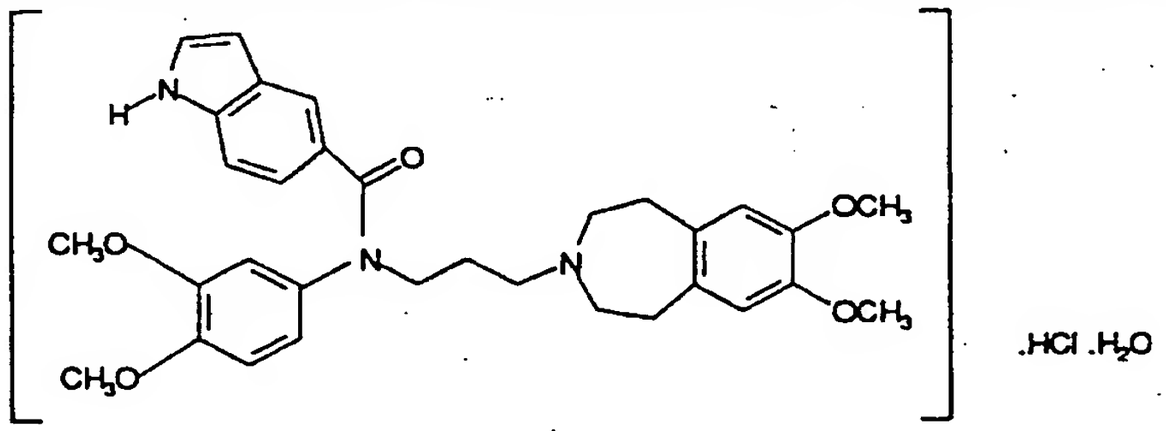
Example 14 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-2-benzofurancarboxamide, hydrochloride, hemihydrate



.HCl .0.5H2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 2-benzofurancarbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 275°C

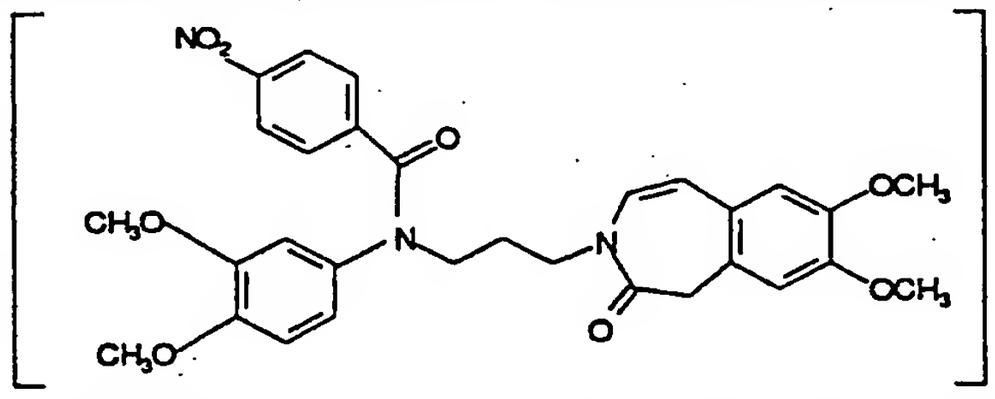
Example 15 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-5-indolecarboxamide, hydrochloride, monohydrate



.HCl .H_2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 1H-indol-5-carbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 165°C

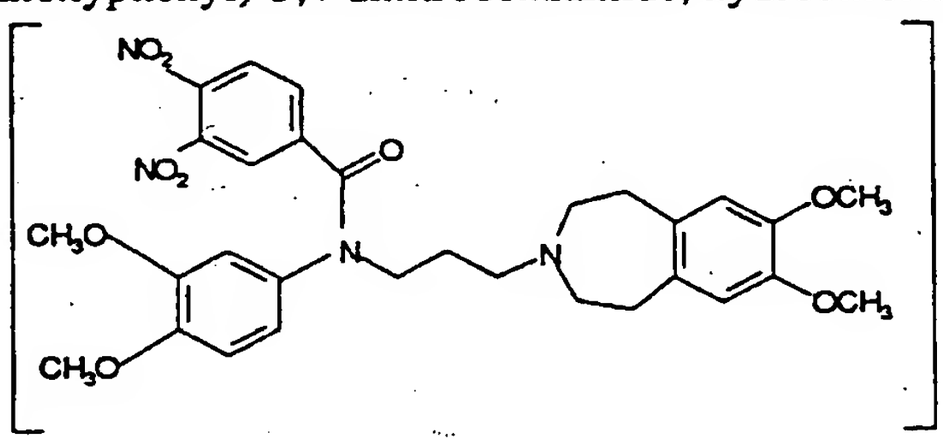
Example 16 N-[3-(7,8-Dimethoxy-2,3-dihydro-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide, monohydrate



.H_2O

Starting from 1,3-Dihydro-7,8-dimethoxy-3-[[(3,4-dimethoxy)phenyl]aminopropyl]-2H-3-benzazepine-2-one (D12) and 4-nitrobenzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 138°C

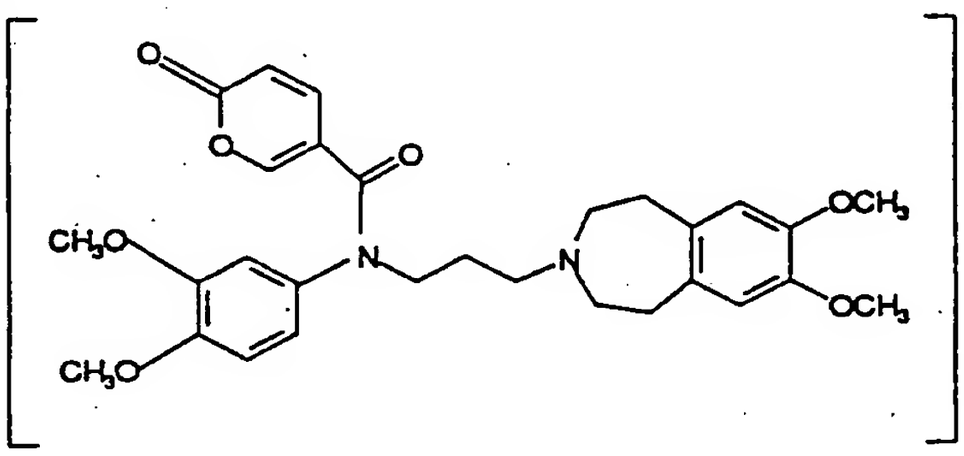
Example 17 N-3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3,4-dinitrobenzamide, hydrochloride, hemihydrate



.HCl .0.5H_2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 3,4-dinitrobenzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 210°C

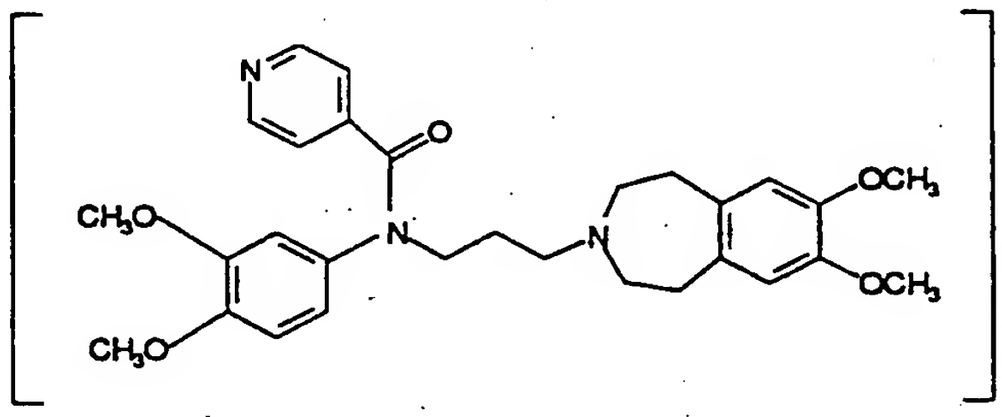
Example 18 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-6-oxo-1H-pyran-3-carboxamide, hydrochloride, hemihydrate



.HCl .0.5H2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 2-oxo-2H-pyran-5-carbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. ~ 190°C

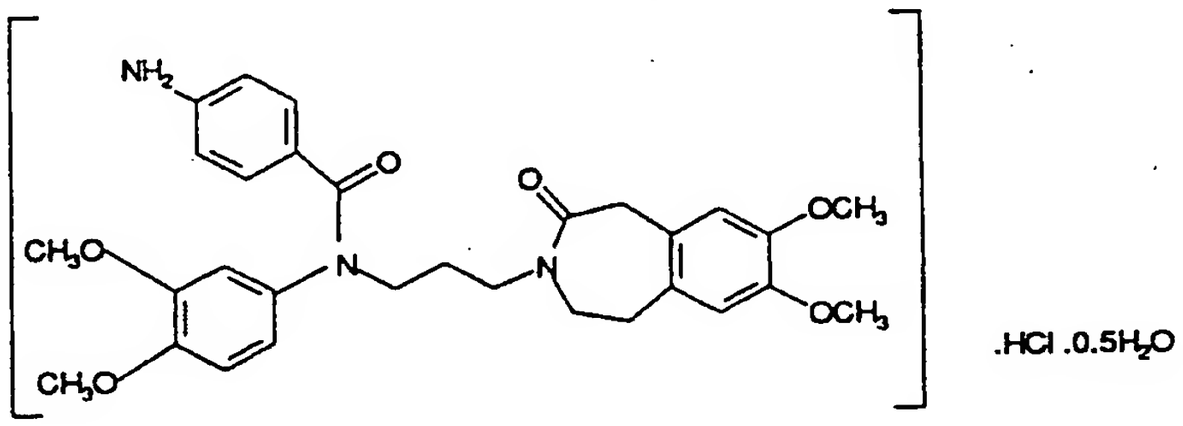
Example 19 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-pyridinecarboxamide, dihydrochloride, hydrate



.2HCl .H2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 4-pyridinecarbonyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. 192°C

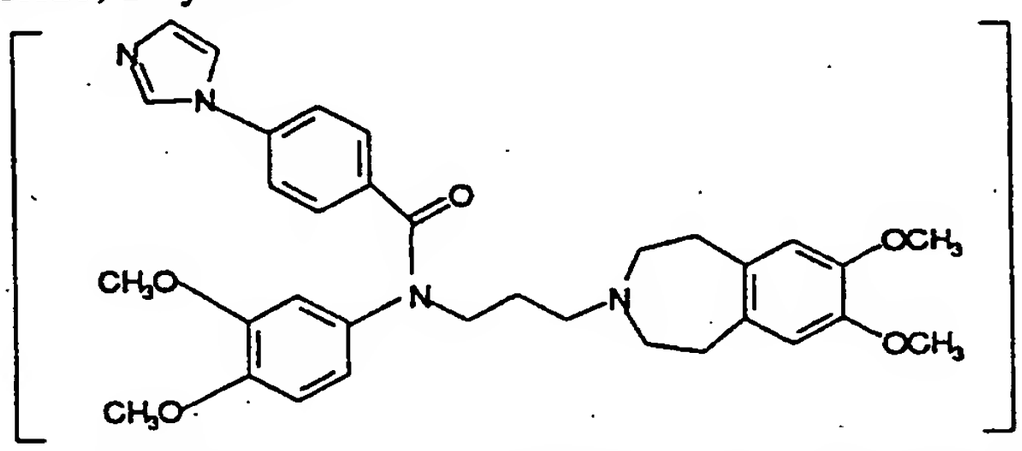
Example 20 4-Amino-N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)benzamide, hydrochloride, hemihydrate



.HCl .0.5H_2O

The title compound was obtained by reduction of the nitro radical of the compound of example 6, using $SnCl_2,H_2O$ in ethanol.
m.p. ~ 135°C

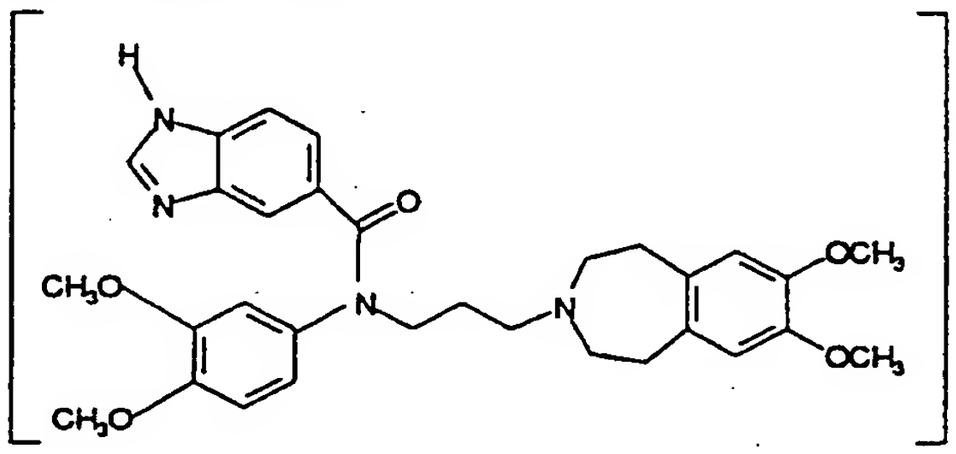
Example 21 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]4-(1H-imidazol-1-yl)--N-(3,4-dimethoxyphenyl)-benzamide, dihydrochloride, dihydrate



.2HCl .2H_2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 4-(1H-imidazol-1-yl)benzoyl chloride and following a method similar to that described in example 1 provided the title compound.
m.p. ~ 185°C

Example 22 N-[3-(2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-1H-benzimidazole-5-carboxamide, dihydrochloride, hemihydrate



.2HCl .0.5H_2O

Starting from 3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-N-(3,4-dimethoxyphenyl) propanamine (D2) and 1H-benzimidazol-5-carbonyl chloride and following a method similar to that described in example 1 provided the title compound.

m.p. ~ 190°C

Pharmacological data

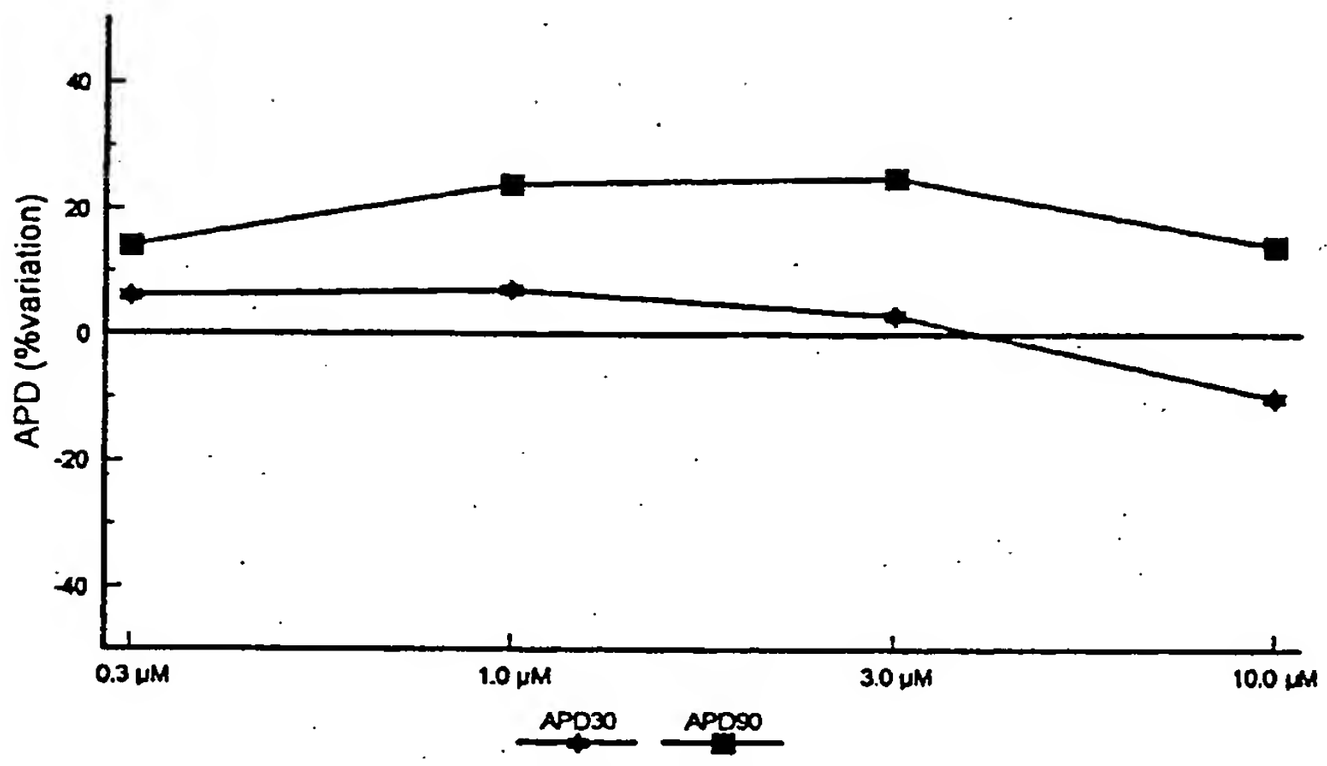
Methodology

Guinea pigs (300-350 g) were anesthetized by intravenous injection of sodium pentobarbital (60 mg/kg). After thoracotomy the heart was rapidly excised and placed in oxygenated Tyrode solution. Papillary muscles were removed from the right ventricle. Preparations were then fixed to the silastic base of a 5 ml organ bath and superfused with oxygenated Tyrode solution maintained at 37 ± 1°C.

The modified Tyrode solution (pH 7.35) contained the following (mM) : NaCl 125, KCl 4.0, $MgCl_2$ 0.5, $CaCl_2$ 1.8, $NaHCO_3$ 24, NaH_2PO_4 0.9 and glucose 5.5. The solution was equilibrated with a gas mixture of 95% O_2 - 5% CO_2.

After a stabilisation period (at least 1h), transmembrane action potentials were recorded with conventional microelectrodes (10 MOhm) connected to a high input impedance amplifier (BIOLOGIC VF 180). External stimuli were delivered to the preparation with bipolar platinum electrodes placed at one end of the muscle. The pulse duration was 1 ms and the amplitude was twice threshold. The basic cycle length was 1000 ms (PULSAR 6i stimulator). The signals were monitored on a storage oscilloscope (GOULD 1602) and simultaneously recorded on a digital tape recorder (BIOLOGIC DTR 1200) for further analysis.

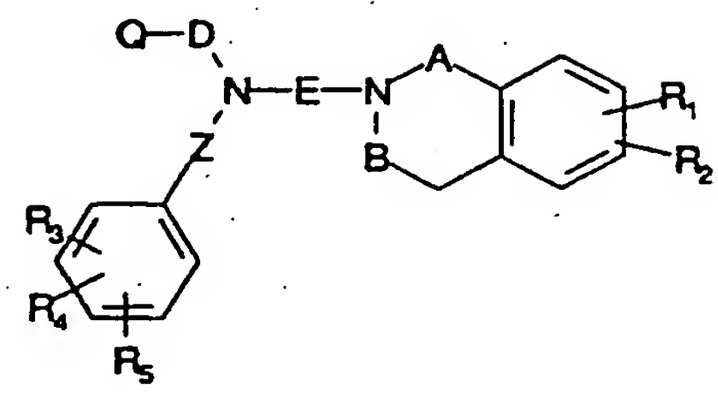
Measurements were made of action potential amplitude (APA) and action potential durations at 30 and 90% repolarization (APD30 and APD90 respectively). Recordings were made after 30 min of equilibration for each concentration. Only recordings in which the same impalement was maintained throughout the entire experiment were used for analysis.



Effect of compound of example 1 on action potential duration (APD) recorded in guinea-pig papillary muscle. Action potential duration was measured at 30% (APD30) and 90% (APD90) of repolarization.

Claims:

1. A compound of formula (I) :



(I)

or a salt thereof, or a solvate thereof, wherein

A represents CH_2, $(CH_2)_2$, CO, $COCH_2$,CH_2CO, $CSCH_2$ or CH=CH;

B represents CH_2 or CO;

Z represents a bond, CH_2, $(CH_2)_2$ or X-CH_2-CH_2 wherein X represents O or S;

D represents CO, SO_2, NH-CO, NH-SO_2,CH=CH or $P(O)OR_6$ wherein R_6 is C_{1-6} alkyl;

Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamide, amino, 1-imidazo, alkyl or haloalkyl, or Q represents substituted or unsubstituted: furanyl, pyranyl, thienyl, thiazolyl, imidazolyl, triazolyl or the benzo fused equivalents of furanyl, pyranyl, thienyl, thiazolyl, imidazolyl or triazolyl, indolyl, oxoindolyl, indenyl, isoindenyl, indazolyl, indolizinyl or pyridinyl or cycloalkyl optionally fused to an aryl group;

R_1, R_2, R_3, R_4 and R_5 each independently represent H, alkyl, OH or alkoxy or, if attached to adjacent carbon atoms, any two of R_1, R_2, R_3, R_4 and R_5 together with the carbon atoms to which they are attached may form a fused heterocyclic ring of four to six atoms wherein one, two or three of the said atoms are oxygen or nitrogen; and

E represents C_{2-4} n-alkylene group wherein each carbon is optionally substituted by R_6 .

2. A compound according to claim 1, wherein Q represents aryl, aralkyl, aralkenyl or aralkynyl, wherein the aryl moiety may be substituted or unsubstituted with 1 to 5 substituents selected from the list consisting of nitro, halogen, alkylsulfonamido, 1-imidazo, alkyl or haloalkyl.

3. A compound according to claim 1 or claim 2, wherein Q represents substituted aryl.

4. A compound according to any one of claims 1 to 3, wherein Q represents nitro phenyl.

5. A compound according to any one of claims 1 to 4, wherein D represents CO, SO_2, NH-CO or -CH=CH-.

6. A compound according to any one of claims 1 to 5, wherein D represents CO.

7. A compound according to any one of claims 1 to 6, wherein A represents CH_2CH_2.

8. A compound according to any one of claims 1 to 7, wherein B represents represents CH_2.

9. A compound according to any one of claims 1 to 8, wherein Z represents a bond.

10. A compound according to any one of claims 1 to 9, wherein R_1, R_2, R_3 and R_2 each independently represent methoxy and R_5 represents hydrogen.

11. A compound according to any one of claims 1 to 10, wherein E represents $CH_2CH_2CH_2$.

12. A compound according to claim 1, selected from the list consisting of:

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3-nitrobenzenesulfonamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-5-nitro-2-furancarboxamide,

N-[3-(78-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl-3-(2-thiophenyl)-3-propenecarboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-7-bicyclo[4.2.0]octa-1,3,5-trienecarboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide,

N-3-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-N'-(4-nitrophenyl)-urea,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-[2-[4-[2-[2-methylpropyl)]phenyl]ethyl]-4-cyanobenzamide,

5-bromo-N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-3-pyridinecarboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-2-oxo-2H-3-benzopyrancarboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-[(3,5-dimethoxyphenyl)methyl]-4-methylsulphonylaminobenzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-[2-(3,4-dimethoxyphenyl)oxy]ethyl]-4-(1H-imidazol-1-yl)benzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-2-benzofurancarboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-5-indolecarboxamide,

N-[3-(7,8-dimethoxy-2,3-dihydro-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide,

N-3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3,4-dinitrobenzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-6-oxo-1H-pyran-3-carboxamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-4-pyridinecarboxamide,

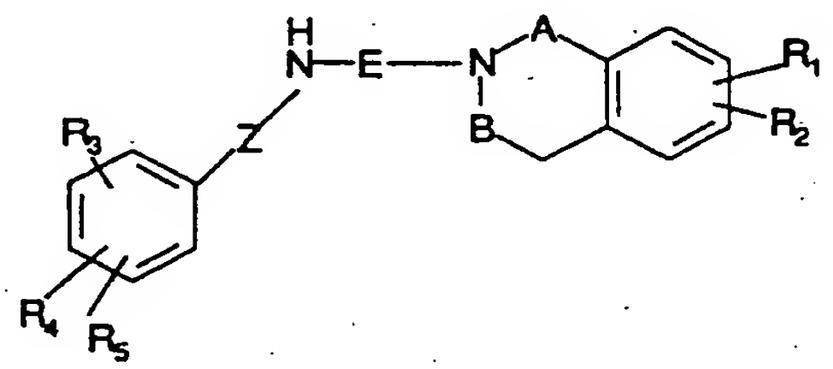
4-amino-N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-2-oxo-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)benzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]4-(1H-imidazol-1-yl)--N-(3,4-dimethoxyphenyl)-benzamide,

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]4-(1H-imidazol-1-yl)--N-(3,4-dimethoxyphenyl)-benzamide, and

N-[3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1H-3-benzazepin-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-1H-benzimidazole-5-carboxamide; or a salt thereof, or a solvate thereof.

13. A process for preparing a compound of formula (I) as defined in claim 1, or a salt thereof, or a solvate thereof, which process is characterised by reacting a compound of formula (II):



(II)

wherein A, B, Z, E, R_1, R_2, R_3, R_4 and R_5 are as defined in relation to formula (I) with a reagent of formula (III):

$$QL^1$$

(III)

wherein Q is as defined in relation to formula (I) and (a) for compounds of formula (I) wherein D is CO or SO_2, L^1 represents COX or SO_2X respectively wherein X is a leaving group such as a halogen, and (b) for compounds of formula (I) wherein D is

NHCO, L^1 is N=C=O; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

14. A pharmaceutical composition comprising a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

15. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

16. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of arrhythmia.

17. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of arrhythmia and ischaemic rhythm disorders.

18. A method for the treatment and/or prophylaxis of arrhythmia and ischaemic rhythm disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

INTERNATIONAL SEARCH REPORT

Interna ıl Application No
PCT/EP 94/01705

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D223/16 C07D217/04 C07D217/24 A61K31/55 A61K31/47
C07F9/6561

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 300 865 (SYNTHELABO) 25 January 1989 see the whole document, particularly page 11, example 40 and page 17, lines 23-25 ---	1-18
Y	EP,A,0 534 859 (ADIR ET COMPAGNIE) 31 March 1993 see the whole document ---	1-18
Y	EP,A,0 065 229 (DR. KARL THOMAE GMBH) 24 November 1982 cited in the application see the whole document ---	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 1994	- 3. 10. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/EP 94/01705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol.33, no.5, May 1990, WASHINGTON US pages 1496 - 1504 M. REIFFEN ET AL. 'Specific bradycardic agents. 1. Chemistry, pharmacology, and structure-activity relationships of substituted benzazepinones, a new class of compounds exerting antiischemic properties' cited in the application see the whole document, particularly page 1498, table V and page 1501, right-hand column, second paragraph	1-18

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I· national application No.
PCT/EP 94/01705

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Interr ...al Application No
PCT/EP 94/01705

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0300865	25-01-89	FR-A-	2618149	20-01-89
		AU-B-	600376	09-08-90
		AU-A-	1907788	19-01-89
		CA-A-	1306748	25-08-92
		DE-A-	3869257	23-04-92
		JP-A-	1034950	06-02-89
		US-A-	5001159	19-03-91
		US-A-	5075325	24-12-91
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		AU-B-	649164	12-05-94
		AU-A-	2533392	01-04-93
		JP-A-	5213890	24-08-93
		NZ-A-	244490	26-07-94
		US-A-	5296482	22-03-94
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		AU-B-	551509	01-05-86
		AU-A-	8379482	25-11-82
		CA-A-	1185239	09-04-85
		GB-A,B	2099425	08-12-82
		JP-B-	1036829	02-08-89
		JP-C-	1554400	04-04-90
		JP-A-	57193462	27-11-82
		SU-A-	1160935	07-06-85
		US-A-	4490369	25-12-84